REMARKS

Amendments to the Specification

The specification has been amended to correct certain informalities. In accordance with 37 C.F.R. § 1.12(b)(1)(i and ii), this Preliminary Amendment includes instructions to replace the title of the application with a replacement title, as well as replace certain paragraphs with replacement paragraphs. Pursuant to 37 C.F.R. § 1.121(b)(1)(iii), marked up versions of the replacement title and paragraphs showing the amendments are provided on separate sheets provided herewith (pages i-v).

The replacement title includes the following amendment:

At page 1, line 1 and page 44, line 1, the word "HIGH" has been replaced with the word "HIGHLY". Support for the amendment of the title can be found throughout the specification, for example, at page 27, line 27-29.

The replacement paragraphs include the following amendments:

At page 7, line 3, "(diamonds)" has been deleted.

At page 30, line 11, "Nitro" has been deleted and "Niro" has been inserted therefor. At line 17, "100 C", "400 C" and 200 C" have been deleted and "100°C", 400°C" and 200°C" have been inserted therefor, respectively. At line 18, "5 C" has been deleted and "5°C" has been inserted therefor. At line 18, the first occurrence of "was determined" has been deleted. At lines 19-20, "50 C" has been deleted and "50°C has been inserted therefor. At line 20, "130 C" has been deleted and "130°C" has been inserted therefor. At line 23, after "geometric diameter", "," has been deleted and "and" has been inserted therefor. At line 23, "and aerodynamic diameter" has been deleted.

At page 31, line 16, "at" has been deleted and "a" has been inserted therefor. At line 21, "particles" has been deleted and "particles'" has been inserted therefor.

At page 32, line 22, "l" has been deleted and "L" has been inserted therefor. At line 26, after the word "sulfate", "and" has been inserted and after the word "compared", "it" has been inserted. At line 28, after the word "primary", "particles'" has been inserted.

At page 33, line 1, after the word "primary", the word "particles'" has been inserted. At line 3, "it's" has been deleted and "its" has been inserted therefor.

At page 35, line 17, "were" has been deleted and "which was" has been inserted therefor. At line 17, "that have" has been deleted and "had" has been inserted therefor. At line 19, "was" has been deleted and "were" has been inserted therefor. At line 22, a space has been inserted between "28.3" and "L/min" and between "2" and "L". At line 24, a space has been inserted between "60" and "L/min".

At page 36, line 4, "lead" has been deleted and "led" has been inserted therefor. At line 7, "be" has been deleted. At line 8, a space has been deleted between "Technetium" and ",". At line 12, "affected" has been deleted and "affect" has been inserted therefor. At line 14, the first "were" has been deleted and "was" has been inserted therefor.

At page 37, line 2, "will be" has been deleted and "was" has been inserted therefor. At line 3, "bay" has been deleted and "by" has been inserted therefor. At line 3, "Than" has been deleted and "Then" has been inserted therefor. At line 4, "will be" has been deleted and "was" has been inserted therefor. At line 8, "were" has been deleted and "was" has been inserted therefor. At line 10, "AIR inhaler" has been deleted and "(AIR inhaler)" has been inserted therefor. At line 10, after the word "and", the phrase "then the inhaler was" has been inserted.

At page 38, line 3, "does" has been deleted and "dose" has been inserted therefor.

Amendments to the Claims

Claims 1, 5-7, 20 and 24-26 have been amended to more clearly define the invention. In accordance with 37 C.F.R. § 1.121(c)(1)(i), this Preliminary Amendment includes instructions to replace Claims 1, 5-7, 20 and 24-26 with the identified replacement claims. Pursuant to 37 C.F.R. § 1.121(c)(1)(ii), a marked up version of these claims showing the amendment is provided on separate sheets provided herewith (page vi-vii).

Claims 1 and 20 have been amended to recite "administering particles comprising a bioactive agent". Support for the particles of the invention comprising a bioactive agent can be found throughout the specification, for example, at page 7, lines 24-25.

Claims 5-7 and 24-26 have been amended to delete "single".

The amendments to the specification and claims are supported by the application as filed. Therefore, this Amendment adds no new matter.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (781) 861-6240.

Respectfully submitted,

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MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the title of the application at page 1, line 1 and page 44, line 1 with the below title, marked up by way of bracketing and underlining to show the changes relative to the previous version of the title.

HIGHLY EFFICIENT DELIVERY OF A LARGE THERAPEUTIC MASS AEROSOL

Replace the paragraph at page 7, lines 3 through 5 with the following paragraph, marked up by way of bracketing and underlining to show the changes relative to the previous version of the title.

Figure 5 is a graph showing the mass deposited in the lungs [(diamonds)] relative to the nominal dose (diamonds). The average deposition for the 10 individuals was 59% (dotted line).

Replace the paragraph at page 30, lines 11 through 21 with the following paragraph, marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

A [Nitro] Niro Atomizer Portable Spray Dryer (Niro, Inc., Columbus, MD) was used to produce the dry powders. Compressed air with variable pressure (1 to 5 bar) ran a rotary atomizer (2,000 to 30,000 rpm) located above the dryer. Liquid feed with varying rate (20 to 66 ml/min) was pumped continuously by an electronic metering pump (LMI, model #A151-192s) to the atomizer. Both the inlet and outlet temperatures were measured. The inlet temperature was controlled manually; it could be varied between 100ºC and 400ºC and was established at 100, 110, 150, 175, or 200ºC, with a limit of control of 5ºC. The outlet temperature [was determined] was determined by the inlet temperature and such factors as the gas and liquid feed rates: it varied between 50ºC and 130ºC. A container was tightly attached to the cyclone for collecting the powder product.

Replace the paragraph at page 30, lines 23 through 24 with the following paragraph, marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The geometric diameter[,] and tap density [and aerodynamic diameter] of the three powders are shown in Table 1.

Replace the paragraph at page 31, lines 13 through 22 with the following paragraph, marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Figure 1 shows the results of this experiment. Applicants have demonstrated that at high pressure, about greater than 2 bars and especially about 3 to 4 bars, all three powders exit the disperser as primary (deaggregated) particles. This supports the finding that [at] a relatively high energy successfully deaggregates all three powders. However at pressures below 2 bars, the micronized powder [Powder 1] exited the orifice in an aggregated state. Evidence of this can be seen by a mean particle size leaving the orifice that was greater than the powder's primary particle size. This was not the case for the spray dried powders [Powders 2 and 3], which emitted from the orifice at approximately their primary particles' size. Powders 2 and 3 were highly dispersible powders.

Replace the paragraph at page 32, line 21 through page 33, line 3 with the following paragraph, marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Using these techniques, the inventors compared the primary size from the dry powder disperser at 4 bar to the emitted size from the AIR inhaler at 30 [l] L/min (Figure 2A). As can be seen, the spray dried hGH and spray dried albuterol sulfate emitted particle size was almost identical to their measured primary particle size, which is not the case for the micronized albuterol sulfate. Finally, the inventors also measured primary and emitted aerodynamic size for the spray dried albuterol sulfate and compared it to the micronized albuterol sulfate (Figure 2B). Again, the spray dried albuterol sulfate emitted with a nearly identical aerodynamic diameter as its primary

particles' aerodynamic diameter while the micronized albuterol sulfate emitted with a much larger aerodynamic diameter than its primary particles' aerodynamic diameter. This further confirms that the spray dried powders of the present invention disperse into respirable particles while the micronized drug remains nonrespirable even though [it's] its primary size is respirable.

Replace the paragraph at page 35, lines 16 through 24 with the following paragraph, marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The placebo powder, comprised of 70/20/10 %w/w DPPC/Sodium Citrate/Calcium Chloride, which was [were] used had [that have] the following characteristics: Dg= 6.7um; ρ=0.06 g/cc; Da= 1.6um. The primary aerodynamic particle size characteristics were [was] obtained using time-of-flight (AeroSizer/AeroDisperser) and the geometric particle size characteristics using laser diffraction (RODOS/HELOS) operated at 1 and 2 bar. Emitted aerodynamic particle size characteristics were obtained using Andersen cascade impaction (gravimetric analysis) operated at 28.3 L/min, for a total air volume of 2 L. Geometric particle size characteristics were obtained using laser diffraction (IHA/HELOS, Sympatec, NJ) operated at 60 L/min.

Replace the paragraph at page 35, line 26 through page 36, line 5 with the following paragraph, marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Placebo powder was filled in a reservoir which was closed by an 0.2 μm filter. A ^{99m}Tc solution (0.5 ml ^{99m}Tc in isotonic saline added to 100 ml of deionized water) was filled in a Pari Jet nebulizer which was placed in a drying chamber. The Pari Jet nebulizer was activated for 3 min to nebulize 1.5 ml of the ^{99m}Tc solution. The particles were dried in this chamber and led [lead] through the reservoir containing the powder. The humidity in the labelling chamber was controlled and never exceeded 30% relative humidity.

Replace the paragraph at page 36, lines 6 through 9 with the following paragraph, marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Because of the short half life of the ^{99m}Tc, the labelling was performed 2 – 4 hours before the inhalation. _The activity of the powder was [be] corrected for the physical decay of the Technetium[ ], to get the actual activity which was available at the beginning of the inhalation.

Replace the paragraph at page 36, lines 10 through 12 with the following paragraph, marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The emitted aerodynamic particle size distribution of the post-labeled powder was obtained using an 8-stage Andersen cascade impactor (gravimetric analysis) to verify that the radiolabeling process did not affect[ed] the particle size distribution.

Replace the paragraph at page 36, lines 13 through 16 with the following paragraph, marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Size 2 capsules were hand filled with 5(±1) mg of the radiolabeled powder. Each capsule <u>was</u> [were] numbered and its filled weight and level of radioactivity were recorded. The subject took a capsule and placed it in the inhaler/spirometer device immediately prior to use.

Replace the paragraph at page 37, lines 1 through 6 with the following paragraph, marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

These 4 ROIs were copied to the gamma camera image of the powder inhalation. _In a region outside of the subject's lung, the background activity <u>was</u> [will be] defined and subtracted pixel <u>by</u> [bay] pixel from the entire image. _[Than] <u>Then</u> the number of counts <u>was</u> [will be] determined for

the 4 ROIs. These numbers were corrected by an attenuation factor for the single regions. After this correction, the relative amount of intrathoracic versus extrathoracic particle deposition was determined.

Replace the paragraph at page 37, lines 7 through 18 with the following paragraph, marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Equivalence between the mass and gamma radiation particle size distributions was obtained, as shown in Figure 4. Approximately 5 mg of powder was [were] loaded into size 2 capsules. The capsules were placed into a breath activated inhaler under development by the applicant (AIR inhaler) and then the inhaler was actuated. Ten healthy subjects inhaled through an inhaler at an approximately inspiratory flow rate of 60 L/min. (The actual inspiratory flow rate varied from subject to subject over a range of 20 to 90 L/min., consistent with the normal range of inspiratory flow rates in humans). 60 L/min is a good average flow rate and is what is used experimentally to mimic inspiratory flow. As measured by a spirometer, the deposition image was obtained using a gamma camera. The percentage lung deposition (relative to the nominal dose) obtained from the ten subjects is shown in Figure 5. The average lung deposition relative to the nominal dose was 59.0%.

Replace the paragraph at page 38, lines 1 through 6 with the following paragraph, marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

The aerodynamic particle size distributions were characterized using a multistage liquid impinger (MSLI) operated at 60 L/min. Size 2 capsules were used for the 6 mg dose [does] and size 000 capsules were used for the 50 mg dose. Figure 6 shows the results comparing the two particle size distributions obtained for the 6 and 50 mg doses. The fine particle fraction, <6.8 μm relative to the total dose (FPF_{TD}<6.8 μm), for the 6 and 50 mg doses were 74.4% and 75.0%, respectively.

Claim Amendments Under 37 C.F.R. § 1.121(c)(1)(ii)

1. (Amended) A method of delivering a therapeutic dose of a bioactive agent to the pulmonary system, in a single, breath-activated step, comprising:

administering particles comprising a bioactive agent, from a receptacle having a mass of particles, to a subject's respiratory tract,

wherein the particles administered to the subject's respiratory tract have a tap density of less than 0.4 g/cm^3 and deliver at least about 50% of the mass of particles.

5. (Amended) The method of Claim 1 wherein the [single] receptacle has a volume of at least about 0.48 cm^3.

6. (Amended) The method of Claim 1 wherein the [single] receptacle has a volume of at least about 0.67 cm^3.

7. (Amended) The method of Claim 1 wherein the [single] receptacle has a volume of at least about 0.95 cm^3.

20. (Amended) A method of delivering a therapeutic dose of a bioactive agent to the pulmonary system, in a single breath, comprising:

administering particles comprising a bioactive agent, from a receptacle having a mass of particles, to a subject's respiratory tract,

wherein the particles have a tap density less than about 0.4 g/cm^3 and deliver at least about 10 milligrams of the bioactive agent.

24. (Amended) The method of Claim 20 wherein the [single] receptacle has a volume of at least about 0.48 cm^3.

25. (Amended) The method of Claim 20 wherein the [single] receptacle has a volume of at least about 0.67 cm^3.

26. (Amended) The method of Claim 20 wherein the [single] receptacle has a volume of at least about 0.95 cm^3.